SEMISOLID DOSAGE FORMS

5. WEEK

SKIN

- ✓ The skin is the largest organ in human body with a surface area of approximately 2 m^2.
- ✓The average thickness of the skin is 1.5 mm, however it may differs by age, gender and anatomic location.
- ✓ Because of its easily accessible large surface area, it has received a great research interest as a noninvasive alternative route to conventional oral or injectable administration of drugs.
- ✓However, it acts as a principal barrier for dermal and transdermal drug delivery.

- ✓ **Skin can be used as a port of entry for therapeutic substances such as drugs and vaccines if the mechanisms that confer the barrier properties are understood.**

Functions of Skin

✓ Mammalian skin has multiple and complex functions.

✓ The major functions of skin are;

- Protecting of the organism against environmental factors
- Regulating body temperature
- Preventing water loss of the body

Functions of Skin

- ✓ One of its main roles is to prevent invasion of the organism by acting as a defensive barrier to threats from the external environment.

- ✓ The skin has evolved defensive mechanisms which give it physical, immunological, metabolic and UV-protective barriers to allow it to inhibit attacks by microorganisms, toxic chemicals, UV radiation and particulate matter (including nanoparticles, which may occur in the natural environment).

Functions of Skin

- ✓ The surface of the skin has been recognised to be acidic, with a pH of 4.2 – 5.6.
- ✓ The surface pH of skin is influenced by gender, anatomical site, sweat, sebum and hydration.
- ✓ This acidic skin surface is described as the acid mantle.
- ✓ The acid mantle has a number of functions, especially including antimicrobial defence.

Structure of Skin

Skin consists of three main layers;

- Epidermis
- Dermis
- Hypodermis (Subcutaneous layer)

Epidermis

The epidermis contains four or five sublayers namely;

-Stratum basale

- Stratum spinosum

- Stratum granulosum

- Stratum lucidum

(It is only in skin of palm and soles)

- Stratum corneum (Horny layer)

Epidermis

- ✓ Epidermis is composed mostly of stratified keratinocytes.
- ✓ Keratinocytes undergo a process of keratinisation, in which the cells differentiate and move upward from the basal layer (stratum basale), through stratum spinosum and stratum granulosum, to the outermost layer, stratum corneum.
- ✓ Cells become flattened and anucleated when they arrive the stratum corneum.

Beyond keratinocytes, distinct type of cells for different functions such as;

- Melanin production (melanocytes)
- Sensory perception (Merkel cells)
- Immunological function (Langerhans cells)

are also present in the viable epidermis.

Stratum corneum

- ✓ The uppermost layer, stratum corneum, is primarily responsible for the barrier function of skin.
- ✓ It consists of corneocytes which are flattened, anucleated and protein-rich cornified cells.
- ✓ Corneocytes are embedded in an extracellular lipid matrix and locked by corneodesmosomes which maintain the structural integrity of stratum corneum.
- ✓ This is often referred to as a 'bricks and mortar' arrangement.

Dermis

Dermis comprises of;

- Connective tissue components
- Nerves
- Blood vessels
- Lymphatics
- Pilo-sebaceous units (hair follicles associated with sebaceous glands)
- Ecrine and apocrine sweat glands

Hypodermis

✓ Hypodermis consists of;

- Cells which produce and store fat

- Main blood vessels

✓ Hypodermis layer provides thermal insulation

Dermal drug delivery

- ✓ Semisolid dosage forms for dermatological drug therapy are intended to produce desired therapeutic action at specific sites of the skin.

- ✓Although some drugs primarily have an impact on the skin surface, the target area for most dermatological disorders is the viable epidermis or upper dermis.

Transdermal drug delivery

Skin is a potential site for the systemic drug delivery.

By this way;

- Some therapeutically active agents can be delivered transdermally with ease
- Hepatic metabolism is avoided
- Constant drug levels in the bloodstream are maintained for longer periods of time
- Potential side effects are decreased
- Patient compliance is increased

Advantages of dermal / transdermal drug application

* The application of drug is easier.

* The active substance is not affected by liver first pass effect.

* The stability of drug which is unstable in gastrointestinal system can be provided.

* Dosage form can be easily removed from skin when a side effect is observed.

Disadvantages of dermal / transdermal drug application

* There is a risk of local allergy and irritation.
* Skin has a low permeability.
* It is not an appropriate route for all of the active substances.

Percutaneous absorption is;

Releasing of active substance from the preparation which was applied to the outer surface of skin and entering microcirculation after penetration through skin layers.

* Dermal and transdermal drug delivery requires efficient penetration of active compounds through the skin barrier basically by a passive diffusion process.

Percutaneous penetration

✓ Percutaneous penetration occurs via passive diffusion.

✓ The permeation of active molecules through the skin can take place by the diffusion;

- Through epidermis (Transepidermal route)
- Through skin appendages (Transappendageal route)

The molecules can cross the intact stratum corneum by two different ways:

- Transcellular route (Intracellular route)
- Intercellular route

The passive diffusion process follows Fick's law.

1st Fick's Law;

$$\frac{dQ}{dt} = -D.A\ \frac{dc}{dx}$$

$$J = \frac{D.K.A.C}{h}$$

dQ / dt = Diffusion rate of the molecule (mg/sn)

dc / dx = Concentration gradient (mg/cm^2)

D = Diffusion coefficient of the molecule (cm^2/sn)

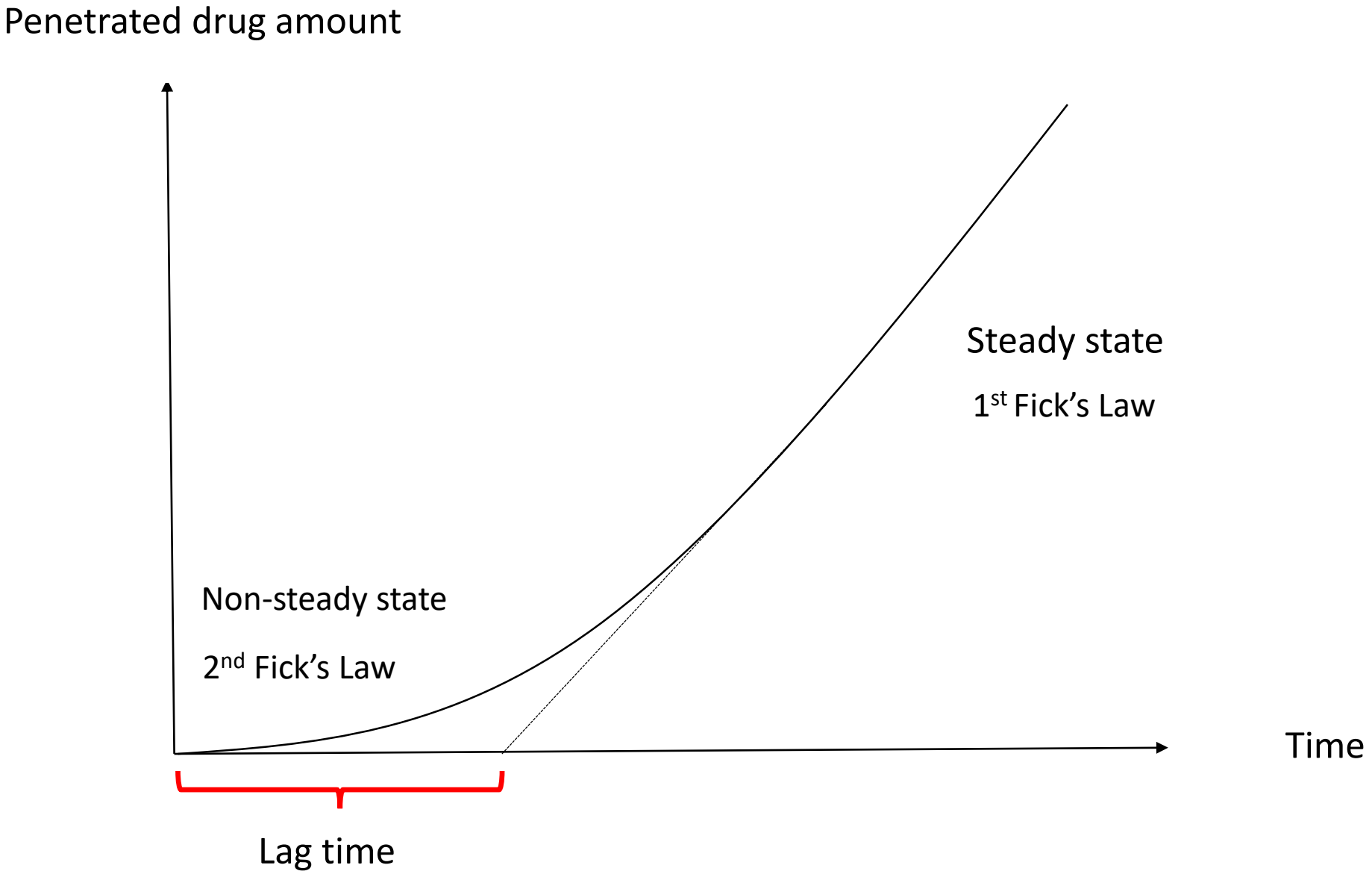
A = Diffusion surface area

J = Penetrated drug amount

K = Partition coefficient of the molecule

h = Layer thickness

Diffusion profile:



SUPPOSITORIES

Why is rectal-vaginal drug delivery preferred?

- General condition of the patient
- GI problems (nausea, etc.)
- Postoperative conditions (patient's state of consciousness)
- Age (pediatric and geriatric patients)
- Disease status (mental disorders)
- Properties of the active substance
- Stability: GI ambient pH, presence of enzymes
- Side effects: GI side effects
- First pass effect
- Taste
- Potential abuse of active substance
- Local + Systemic effect
- Application and removal of the dosage form is painless and safe
- The duration of drug action can be extended and designed with appropriate formulations

Disadvantages:

- Slow and sometimes insufficient absorption of active agents
- Absorption differs among individuals
- Long-term rectal drug use may cause proctis (inflammation of the rectum wall) development
- Cultural and traditional beliefs
- Problems with the large scale production of suppositories and obtaining appropriate shelf life

Rectal-Vaginal Dosage Forms

- Suppositories
- Rectal capsules
- Rectal solutions
- Emulsions and suspensions
- Tablets and powders for rectal solutions and suspensions
- Semi-solid rectal preparations
- Foams

Suppository

- Different shaped (conical, cylindrical, globular) and sized (usually from 1-4 g) solid or semi-solid preparations that contain one or more active agents dispersed or dissolved in a suitable base (water-soluble or dispersible or soluble in body temperature). Usually medicated, for insertion into the rectum, vagina, or urethra.

- The content of the active agent ranges from 0.1% to 40%.

Rectal Route

Local effect

It is mostly used for the treatment of local pain and itching caused by hemorrhoids.

Astringent, antiseptics, local anesthetics, vasoconstrictors, anti-inflammatory compounds and sedative and protective agents, laxatives

Systemic effect

Anti-asthmatic, anti-inflammatory and analgesic drugs are commonly administered rectally. Rectal preparations can also be used for diagnostic purposes.

Peptide drugs

Rectal Absorption

- Absorption of active substances from the rectum is mainly by passive diffusion. The bioavailability of drugs after rectal administration is very uncertain due to individual differences between patients and rectal venous drainage of the rectum. In general, the rate and amount of absorption of the active ingredients is lower than the oral route due to the small surface area for absorption.
- Venous drainage of the rectum is important for understanding the absorption of active substance:
- Lower and middle rectal (inferior and middle hemorrhoidal) vessels flow into the inner vena cavity, so this blood goes directly to the heart and into the general circulation. Whereas,
- The upper rectal (superior hemorrhoidal) vein flows into the portal vein and therefore passes through the liver before it reaches the heart.

- This means that the drug molecules from the rectum can enter the general circulation directly or through the liver. In the middle and lower part of the rectum, the absorbed drug will pass directly into the general circulation and prevent first-pass metabolism in the liver. Bioavailability from the upper part of the rectum will be low for some drugs, because they will be metabolized by the liver during the 'first passage' and only some of the drug molecules will enter to general circulation intact.

- Studies have shown that it is possible to prevent the first passage from the liver by keeping the released drug in the lower part of the rectum.

- Applying a suppository to the rectum results in a chain of events leading to absorption of the active agent. Depending on the character of the suppository base, the suppository dissolves in the rectal fluid or melts in the mucus layer.

- Since the volume of the rectal fluid is very small, it will be difficult to dissolve all the fluids and require extra water. Due to osmotic effects, the water absorbs when it dissolves and creates an unpleasant feeling for the patient.

- Regardless of the base type, the active substance dissolved in the suppository is dispersed towards the rectal membranes.

- If the active substance is suspended on the suppository base, initially it is released under the influence of gravity or motility and then begin to dissolve in the rectal liquid.
- Soluble active substance molecules diffuse from the mucus layer and then from the epithelium forming the rectal wall.
- Absorption occurs by passive diffusion.
- The active transport mechanism in the upper regions of the gastrointestinal tract is not present in the rectal region.

Factors of Suppository Base Affecting Absorption from the Rectum

- Melting point of base,
- The solubility of the base in the fluids of the application area
- The solubility of the active agent in base,
- Characteristics of the release of the active agent from the base
- Spreading property of the base.
- Viscosity of the base (etc.).

Factors of Active Agent Affecting Absorption from Rectum

- Solubility of active agent in water
- The degree of ionization and pKa of the active agent
- Solubility of the active agent in lipids / partition coefficient
- Particle size of active agent